

## **EXHIBIT 1, Tab 3**

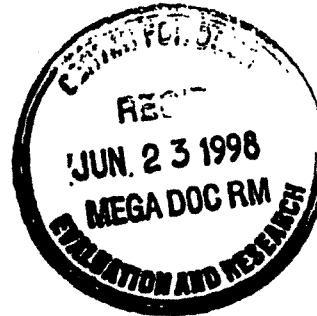


Quintiles BRI  
Strategic Regulatory Division  
1801 Rockville Pike, Suite 300  
Rockville, MD 20852  
301 530 9222 / 301 272 2150 Fax  
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June 23, 1998

VIA COURIER

Division of Anti-Inflammatory, Analgesic,  
and Ophthalmologic Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-550  
9201 Corporate Boulevard  
Rockville, MD 20850



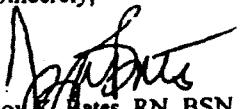
Attn: Ms. Sandra Cook, Project Manager  
Subject: Information Amendment: Biopharmaceutical Information  
NDA 20-905  
Serial No. 025

Dear Ms. Cook:

Enclosed please find two copies of the NDA amendment to report Biopharmaceutical Information regarding the use of 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet as the loading dose regimen for Leflunomide. A report is appended to this amendment to provide comparative in vitro dissolution data. This issue was discussed in a teleconference on May 29, 1998 between Dr. Mark Eller of Hoechst Marion Roussel, Inc. (HMR) and Dr. Dennis Bashaw of the FDA.

If you have any questions regarding the above information, please do not hesitate to contact me at (301) 272-3122.

Sincerely,

  
Joy K. Bates, RN, BSN  
Manager, Regulatory Affairs  
Strategic Regulatory Division

Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		Form Approved OMB No. 0910-0239 Expiration Date: April 30, 2000 See OMB comment on page 2.
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE (Title 21, Code of Federal Regulations, 314 & 601)		
<b>APPLICANT INFORMATION</b> <b>NAME OF APPLICANT</b> Hoechst Marion Roussel, Inc. <b>TELEPHONE NO. (Include Area Code)</b> (816) 966-7297		<b>DATE OF SUBMISSION</b> JUN 26 1998 <b>FACSIMILE (FAX) NUMBER (Include Area Code)</b> (816) 966-3594
<b>APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):</b> 10236 Marion Park Drive Kansas City, MO 64137		<b>AUTHORIZED U.S. AGENT NAME &amp; ADDRESS (Number, Street, City, State, ZIP Code, telephone &amp; FAX number) IF APPLICABLE</b> Quintiles BRI, Inc. 1801 Rockville Pike, Suite 300 Rockville, MD 20852 (301) 530-9222 FAX (301) 272-2150
<b>PRODUCT DESCRIPTION</b> <b>NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)</b> <b>ESTABLISHED NAME (e.g., Proper name, USP/USAN name)</b> leflunomide (INN, USAN pending) <b>CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)</b> N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide HWA 486, A77 <b>DOSE FORM:</b> Immediate Release Film-Coated Tablets <b>STRENGTHS:</b> 10mg, 20mg, 100mg. <b>ROUTE OF ADMINISTRATION:</b> Oral Tablets <b>(PROPOSED) INDICATION(S) FOR USE:</b> Rheumatoid Arthritis		
<b>APPLICATION INFORMATION</b> <b>APPLICATION TYPE</b> (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601) <b>IF AN NDA, IDENTIFY THE APPROPRIATE TYPE</b> <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507 <b>IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION</b> Name of Drug Holder of Approved Application		
<b>TYPE OF SUBMISSION</b> (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
<b>REASON FOR SUBMISSION</b> Proposal for alternative loading dose regimen.		
<b>PROPOSED MARKETING STATUS</b> (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
<b>NUMBER OF VOLUMES SUBMITTED</b> 1 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
<b>ESTABLISHMENT INFORMATION</b> Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
<b>Cross References</b> (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		

This application contains the following items: (Check all that apply)

1. Index		
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))		
4. Chemistry section		
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)		
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)		
5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)		
6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)		
7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))		
8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)		
9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)		
10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)		
11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)		
12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)		
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))		
14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (f) (2) (A))		
15. Establishment description (21 CFR Part 600, if applicable)		
16. Debarment certification (FD&C Act 306 (k)(1))		
17. Field copy certification (21 CFR 314.50 (k) (3))		
18. User Fee Cover Sheet (Form FDA 3397)		
19. OTHER (Specify)		

#### CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Douglas M. Hunt, Director QSRD	DATE 6/23/78
ADDRESS (City, State, and ZIP Code) 1801 Rockville Pike, #300, Rockville, MD 20852	Telephone Number (301) 530-9222	

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NDA #20-095  
Serial No. 025

**Leflunomide Tablets**  
**Hoechst Marion Roussel, Inc.**

## **Leflunomide Tablets**

**NDA Amendment/Biopharmaceutical Information**

**NDA #20-095  
Serial No. 025**

**Hoechst Marion Roussel, Inc.  
10236 Marion Park Drive  
Kansas City, Missouri 64137-1405**

NDA #20-905  
Serial No. 025

Leflunomide Tablets  
Hoechst Marion Roussel, Inc.

## 1.0 Introduction and Background

The original New Drug Application (NDA) # 20-905 for Leflunomide Tablets was submitted to FDA on March 10, 1998 for the indication of Rheumatoid Arthritis. The NDA proposed a loading dose of 1 x 100 mg tablet for 3 days followed by maintenance doses of 10 mg or 20 mg per day. Tablets of all 3 strengths (10 mg, 20 mg, and 100 mg) are included in the NDA.

Reference is made to a teleconference on May 29, 1998 between Dr. Mark Eller of Hoechst Marion Roussel, Inc. (HMR) and Dr. Dennis Bashaw of the FDA. The objective of the teleconference was to explore the possibility of using 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet as the loading dose regimen.

The 100 mg tablets were used in the pivotal Phase III studies for the loading dose of 100 mg QD for the initial 3 days of therapy. The sponsor does not plan to withdraw the 100 mg tablet from the NDA, but would like to propose the use of 5 x 20 mg tablets QD for 3 days as an alternate regimen for administration of the 100 mg loading dose for Leflunomide Tablets.

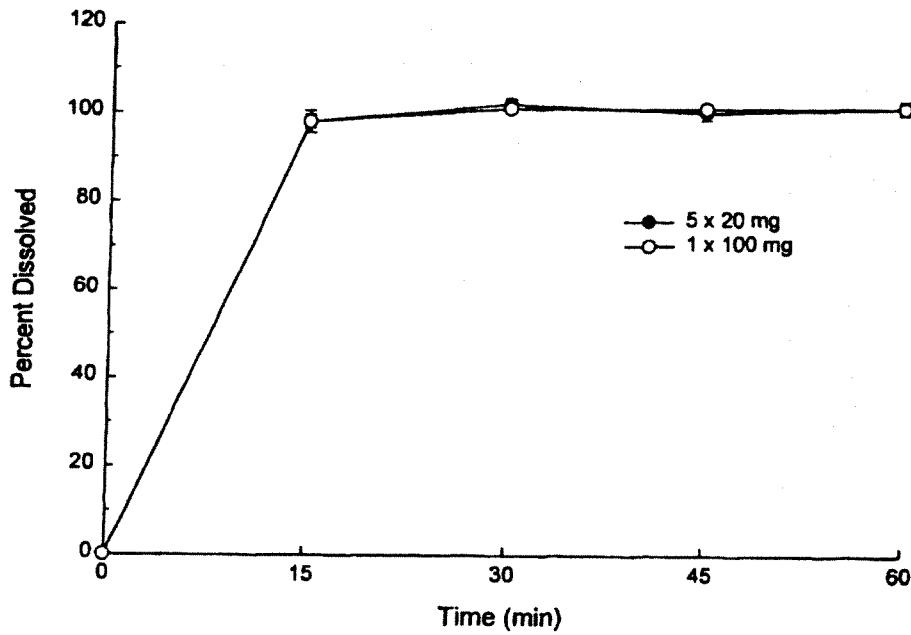
The efficacy of leflunomide is related to the steady-state plasma concentrations of A77 1726, the primary metabolite. The steady-state plasma concentrations are a function of the maintenance dose, not the loading dose. Assuming a given maintenance dose, equivalent steady-state concentrations would be achieved from either a 1 x 100 mg or 5 x 20 mg tablet loading dose.

We support our proposal with in vitro dissolution data and a clinical justification, which are discussed in Sections 2.0 and 3.0, respectively.

NDA #20-095  
Serial No. 025Leflunomide Tablets  
Hoechst Marion Rousset, Inc.

## 2.0 In Vitro Dissolution Data

Document No. PDK12848/98 (Appendix I) compares the composition of the 20 mg and 100 mg tablets (U.S. commercial formulations) and their in vitro dissolution profiles. Using the in vitro dissolution system proposed for the 100 mg tablet, the dissolution profiles for 1 x 100 mg and 5 x 20 mg tablets were superimposable (Figure 1) and met the current specifications for the 100 mg tablet (i.e.,  $\geq 70\%$  (Q) at 30 min).



**Figure 1: In Vitro Comparative Dissolution Profile**

## 3.0 Clinical Justification

Leflunomide, the active chemical entity in Leflunomide Tablets, is rapidly metabolized to A77 1726, the pharmacologically active compound in man. A77 1726 has an elimination half-life of 15 to 18 days in patients with rheumatoid arthritis. A regimen of 100 mg/day as

NDA #20-095  
Serial No. 025Leflunomide Tablets  
Hoechst Marion Roussel, Inc.

a single dose for the first 3 days of therapy is therefore recommended as a loading dose to decrease the time required to reach steady-state. Clinical efficacy is dependent upon the steady-state concentrations and those are a function of the maintenance rather than the loading dose. Consequently, any differences in absorption that may exist between a 100 mg dose administered as 1 x 100 mg tablet or 5 x 20 mg tablets would not alter the therapeutic effect.

#### **4.0 Conclusion**

We propose to use 5 x 20 mg tablets as an alternative to 1 x 100 mg tablet for the 100 mg QD x 3 days loading dose proposed in the NDA. Based on the following points, we feel that the two loading dose regimens are comparable:

- the in vitro dissolution profiles of 1 x 100 mg tablet and 5 x 20 mg tablets are equivalent;
- the elimination half-life of the major metabolite (A77 1726) is 15 to 18 days; a loading dose of 100 mg QD for the initial 3 days is recommended only to decrease the time required to reach steady-state; and
- clinical efficacy is dependent upon the steady-state concentrations achieved by the maintenance dose and not the loading dose.

#### **5.0 FDA Concurrence**

Based on the information submitted in this NDA amendment, we respectfully request that FDA consider the following:

- 1) Does FDA concur with the conclusions stated in section 4.0 above?
- 2) Does FDA agree that the loading dose of 100 mg can be administered either as 5 x 20 mg tablets or 1 x 100 mg tablet?
- 3) Does FDA concur that an in vivo bioequivalence study between 1 x 100 mg and 5 x 20 mg tablets is not warranted?

NDA #20-095  
Serial No. 025

Leflunomide Tablets  
Hoechst Marion Roussel, Inc.

**Appendix I: Document No. PDK12848/98**

**Comparative Dissolution of Two Different Dosage Strengths**

**HWA 486 Film-coated Tablets: 20 mg, 100 mg**

**Hoechst Marion Roussel**

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HWA 486 Film-coated Tablets:  
20 mg, 100 mg

Comparative Dissolution of Two Different Dosage Strengths

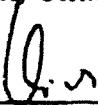
Document No.: PDK12848/98

May 13, 1998

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This report contains the unpublished research findings of Hoechst scientists. It should not be published in whole or in part or referred to in any publication without authorization from the company.

HMR Global Pharmaceutical Development Germany,  
Analytics, Germany

  
\_\_\_\_\_  
Quality Control Manager  
(Dr. Schmidt)

  
\_\_\_\_\_  
Head of Laboratory  
(Dr. Loos)

**Hoechst Marion Rousset**


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**HWA 486 Film-coated Tablets:** Comparative Dissolution of Two Different Dosage Strengths  
20 mg, 100 mg

Document No.: PDK12848/98

May 13, 1998

**1. Objective**

HWA 486 film-coated tablets are designed as immediate-release tablet formulations containing 10 mg, 20 mg and 100 mg leflunomide.

The aim of this document is to compare the dissolution profile of five HWA 486 film-coated tablets of 20 mg dosage strength with the dissolution profile of one 100 mg tablet.

In addition comparative data are provided on individual 20 mg tablets being tested under the same conditions.

**2. Composition of Tablets**

Two fullscale commercial batches were used for the tests. The composition of the batches is given in the table below.

Strength	20 mg	100 mg
Batch No.	L113B	33
<u>Tablet (mg)</u>		
Leflunomide	20.000	100.000
Lactose monohydrate	72.000	138.400
Maize starch	46.000	86.300
Povidone, Type K25	3.500	7.380
Cropovidone	7.500	18.450
Talc	---	15.500
Colloidal anhydrous silica	0.500	1.110
Magnesium stearate	0.500	1.840
Mass of tablet (mg)	150.000	369.000
<u>Film coating (mg)</u>		
HPMC	2.516	5.443
Macrogol 8000	0.160	0.288
Titanium dioxide (E 171)	0.629	1.361
Talc	0.189	0.408
Yellow ferric oxide	0.006	---
Mass of film coating (mg)	3.500	7.500
Mass of film coated tablet (mg)	153.000	376.500

**Hoechst Marion Roussel**

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**HWA 486 Film-coated Tablets:** Comparative Dissolution of Two Different Dosage Strengths  
20 mg, 100 mg

Document No.: PDK12848/98

May 13, 1998

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**3. Test Conditions**

Tablet strengths: 20 and 100 mg

Test conditions (based on the control test for HWA 486 film-coated tablets 100 mg):

Apparatus: Paddle (USP Apparatus 2)

Speed of rotation: 100 rpm

Dissolution medium: Water containing 0.6% (m/V) of polyoxyethylene lauryl ether (e.g. Brij®35, Riedel-de-Haen article no. 33059), 1000 ml

Time: 15, 30, 45 and 60 min

Method:

Remove dissolved gases from the dissolution medium by means of a vacuum before the test since they can cause the formation of bubbles which significantly affect the results.

Place 1000 ml of the dissolution medium in the vessel, assemble the apparatus, warm the dissolution medium to  $37 \pm 0.5^{\circ}\text{C}$  and remove the thermometer.

Place one 20 mg tablet, five 20 mg tablets or one 100 mg tablet in each of six vessels at the bottom before starting rotation of the blade. Take care to avoid the presence of air bubbles on the surface of the sample. Start the rotation of the apparatus with 100 rpm immediately after the sample has sunk to the bottom.

At specified time intervals samples are withdrawn and replaced by fresh dissolution medium.

The maximal permissible deviation from the rotation speed amounts to  $\pm 4\%$ .

Determination of dissolved leflunomide:

Determine the amount of dissolved leflunomide by UV/VIS spectroscopy.

Test solution: Withdraw 10.0 ml after the specified time intervals from a position midway between the surface of the dissolution medium and the top of the blade and not less than 10 mm from the vessel wall. Dilute the sample to 100.0 ml with water containing 0.6 % (m/V) of polyoxyethylene lauryl ether in case of the test with five 20 mg tablets and one 100 mg tablet. Dilute the sample to 25.0 ml with water containing 0.6 % (m/V) of polyoxyethylene lauryl ether in case of the test with one 20 mg tablet.

**Hoechst Marion Roussel**

**HWA 486 Film-coated Tablets:** Comparative Dissolution of Two Different Dosage Strengths  
20 mg, 100 mg

Document No.: PDK12848/98

May 13, 1998

**Standard solution:** Dissolve 20.0 mg of leflunomide reference standard in methanol and dilute to 50.0 ml with the same solvent. Dilute 2.0 ml of the solution thus obtained to 100.0 ml with water containing 0.6 % (m/V) of polyoxyethylene lauryl ether.

**Wavelength:** 262 nm (maximum of absorbance)

**Blank value:** Measurement of the test solution: Water containing 0.6 % (m/V) of polyoxyethylene lauryl ether.  
Measurement of the standard solution: Dilute 2.0 ml methanol to 100.0 ml with water containing 0.6 % (m/V) of polyoxyethylene lauryl ether.

The specific absorption A (1%, 1 cm) of leflunomide in the dissolution medium is approximately 690.

#### 4. Results

Table 1: Dissolution of one 20 mg HWA 486 film-coated tablet in each vessel

Time [min]	Percent dissolved						Mean [%]	Range [%]	SD
	1	2	3	4	5	6			
15	86	91	89	90	87	89	89	86- 91	1.7
30	99	101	96	98	98	97	98	96-101	1.6
45	100	101	96	98	97	96	98	96-101	2.2
60	100	100	96	99	98	98	99	96-100	1.4

Table 2: Dissolution of five 20 mg HWA 486 film-coated tablets in each vessel

Time [min]	Percent dissolved						Mean [%]	Range [%]	SD
	1	2	3	4	5	6			
15	99	100	96	99	97	99	98	96-100	1.5
30	103	102	102	102	99	102	102	99-103	1.3
45	102	101	99	97	99	102	100	97-102	1.7
60	103	102	101	100	99	102	101	99-103	1.5

**Hoechst Marion Roussel**

HWA 486 Film-coated Tablets: Comparative Dissolution of Two Different Dosage Strengths  
20 mg, 100 mg

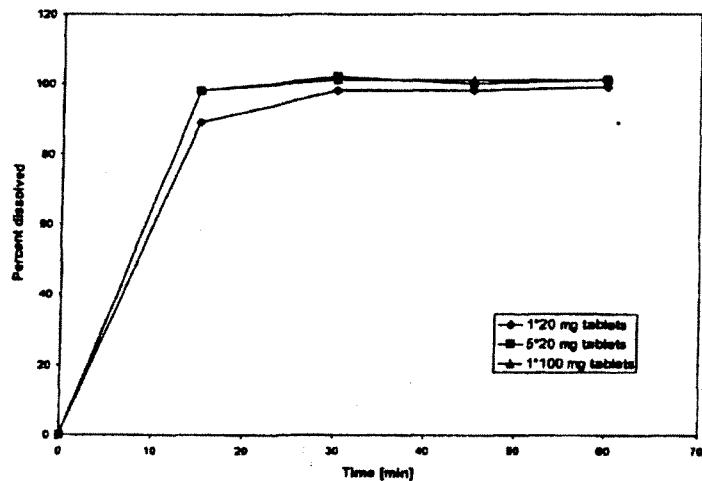
Document No.: PDK12848/98

May 13, 1998

Table 3: Dissolution of one 100 mg HWA 486 film-coated tablet in each vessel

Time [min]	Percent dissolved						Mean [%]	Range [%]	SD
	1	2	3	4	5	6			
15	94	98	100	101	99	99	98	94-101	2.5
30	101	102	100	102	101	101	101	100-102	0.8
45	101	102	101	102	101	100	101	100-102	0.9
60	100	102	101	102	101	99	101	99-102	1.1

Figure 1: Comparative dissolution of the different dosage strengths

**5. Discussion**

The dissolution of HWA 486 film-coated tablets goes rapidly and completely irrespective of the investigated dosage strength.

All test samples comply with the current requirements of the specifications set for the 100 mg tablets.

The dissolution profiles of one 20 mg tablet in each vessel, five 20 mg tablets in each vessel and one 100 mg tablet in each vessel are comparable.